A CLINICAL LECTURE ON THE SLEEPING SICKNESS

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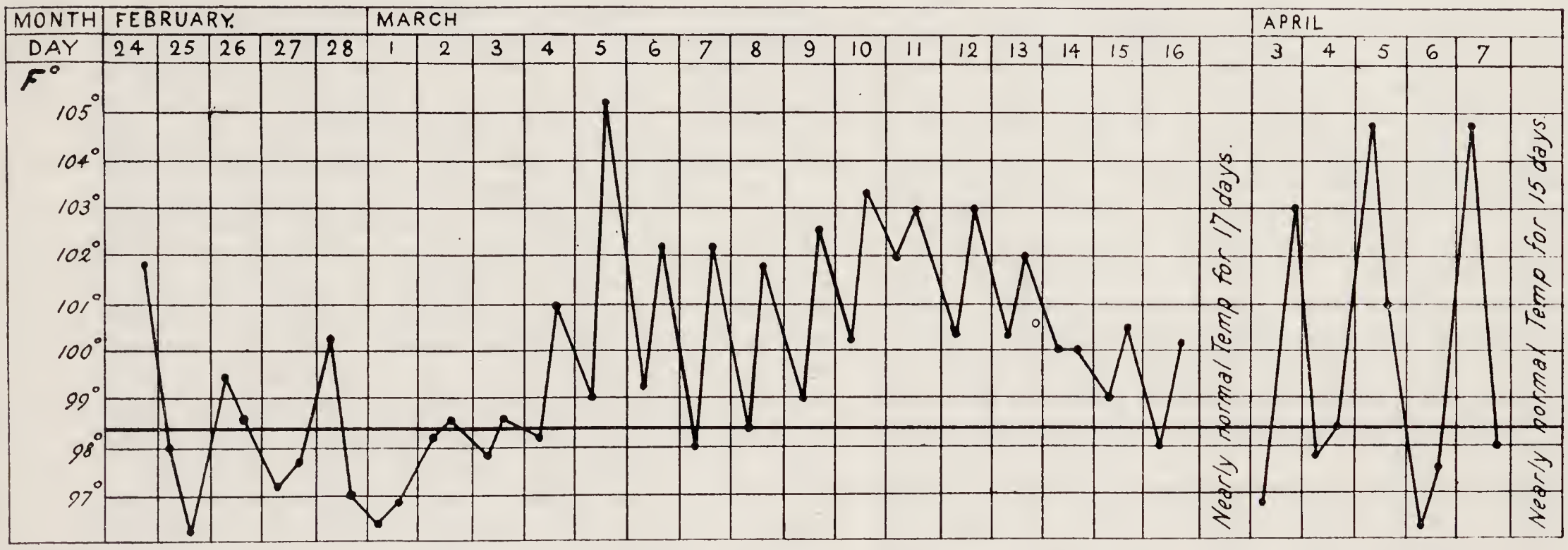
one of emaciation, the spleen could not be felt, and Widal's reaction gave a positive result. At the end of the month the temperature suddenly went up to 103° and he had a typical malaria rigor; the temperature fell again to rise two days later, when another rigor occurred—the spleen could then be felt. Amœboid



pigmented parasites (benign tertian) nearly filling the corpuscles and enlarging them, and some flagellated bodies were found on examining the blood. After the occurrence of three rigors, quinine was commenced again in doses of five grains every six hours.

When the temperature was due to rise for the next paroxysm no parasites could be found in the blood, and the spleen had diminished in size. Quinine was continued until a drachm had been taken; then iron and arsenic pills were substituted for the quinine, except on Sundays.

The patient left the hospital on April 22, having had a nearly normal temperature for a fortnight.

Comments.—The combination of most of the ordinary clinical signs of enteric fever, such as headache, abdominal distension, crops of rose spots, enlarged spleen, yellow stools and slight bronchitis with a repeated positive result to Widal's test, even in spite of the absence of a quite typical chart (of which the atypical character is probably due in some measure to the administration of quinine), and of a quite typical tongue (which was moist and furred throughout the illness), will, I think, be taken as sufficient evidence of enteric fever.

Positive proof was given by the microscope of the presence of the malarial parasite, both before and after the occurrence of the enteric fever.

The case might be described as one of typho-malaria; the expression being used not as indicating a specific disease, but as Dr. Manson says, as indicating "an ordinary typhoid occurring in an individual who has been exposed to malarial influences."

Of the three clinical types of cases he describes this case will come partly under the first and partly under the last. Osler says: "Of nearly four hundred cases of typhoid fever, all with blood examinations and a majority of them coming from malarial regions, in not a single instance were the malarial parasites found in the blood."

The behaviour of the spleen in the case is of interest. I have no note of its condition when the patient was admitted; but it evidently enlarged from the enteric fever in spite of the administration of quinine, and later when the enteric fever was over enlarged again from the malaria and was controlled by quinine.

A CLINICAL LECTURE ON THE SLEEPING SICKNESS.

Delivered at Charing Cross Hospital, October, 1898.

By Patrick Manson, M.D., LL.D., F.R.C.P.

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Gentlemen,—I propose to speak to you this afternoon about the two negro boys who have been in Alexandra Ward for the last few weeks. They come from a village called Mbanza Manteka, on the Lower Congo, and were brought to England principally through the instrumentality and enlightened benevolence of Dr. Grattan Guinness and the missionary body he represents. They were brought to this country partly that they might have the chance of treatment under conditions more favourable than any their own homes could supply, partly that they might afford an opportunity for careful study of the deadly disease from which they are suffering. Although it is not likely that any of you, unless you visit the West Coast of Africa, will ever see similar cases again, nevertheless, their study is capable of affording useful lessons of a practical character. Apart from such practical consideration there is much about these cases of theoretical interest. If the medical student aspires as he should aspire, to be a student of medicine, he must be catholic, and embrace in his studies all forms of disease, no matter though some of these diseases happen to be confined to a limited geographical area, no matter though they affect only what we, in our pride, consider an' inferior race. The science of pathology embraces black men as well as white men; the principles of pathology are the same for all.

Nomenclature.

The disease from which these negro boys are suffering is called the "sleeping sickness;" sometimes, and because it is especially prevalent there, the

"sleeping sickness of the Congo;" sometimes "negro lethargy." A better name would be "African lethargy."

Geographical Limits.

It has a singularly limited geographical distribution, being, so far as we at present know, absolutely confined to that part of West Africa which lies between the Senegal to the north and Loanda to the south, some 1,500 miles of latitude. It extends into the back country; how far it is difficult to say. I am told by Dr. Sims, of Stanley Pool, who has had many years' experience of Congoland, that it occurs as far up the Congo as Stanley Falls, that is to say, to the very centre of equatorial Africa. So that, after all, the geographical limitations are not so restricted. The area involved, though large, like everything that is at a distance from us, bulks small in the mind's eye. It probably exceeds that of Europe; it certainly carries a population of several tens of millions.

Although widely diffused throughout this huge region, fortunately for the inhabitants, it is only here and there, in certain circumscribed spots, in certain villages, or groups of villages, that sleeping sickness occurs as an endemic affection. Nor is it always equally prevalent in these places. In the spots affected it seems to come and go, to wax and wane as it were. And it is fortunate that it is so; for, when sleeping sickness breaks out in a community it attacks a large proportion of the members of that community, and all who are attacked surely die.

Mortality in Epidemics.

Thus in the village from which these boys come, out of a Christian congregation of about 1,000 last year 28 died of sleeping sickness; and this year, Mr. Richards tells me (it was Mr. Richards who brought these boys home), that up to the month of August, when he left the Congo, out of a congregation of about 1,150, 28 had already died, a mortality at the rate of about 40 per annum. Corre, a French writer, who studied the disease in Senegambia, tells us that in some districts of the Lower Senegal it sweeps away whole villages at a time, half the people dying, the remainder fleeing from the pestilence.

Racial Proclivity.

Hitherto we have no well authenticated account of the disease in a white man; doubtless, however, were the white man exposed to the cause, whatever this may be, he would prove as susceptible as the negro. It has been met with in half-breeds and in Moors. Some have suggested that sleeping sickness is in some way inherent and peculiar to the negro, a sort of ethnic disease. This cannot be the case, for the negroes of the States, of the West Indies and of Brazil, and the natives of north, east, and south Africa never, so far as we know, nowadays get the disease. I say nowadays, because formerly, in the old evil times of the slave trade, sleeping sickness was well known on the plantations in the West Indies; but it was then known only as an imported disease. It never attacked negroes born on the plantations, only those who had been kidnapped in Africa. It did not spread on the plantations, or become domiciled, as it were, in America. I beg of you to note this circumstance; it is an important one to keep in mind in connection with the question of etiology.

Prolonged Latency.

Another significant fact about the disease is that it may remain latent for years—as long as seven years it is said. Thus, in the evil times I refer to, what appeared to be a healthy slave might be landed in the West Indies, and might do excellent work for his owner for several years, and then, without apparent reason, he would begin to exhibit symptoms of sleeping sickness, and by-and-by die of the disease.

Some years ago a little Congo boy was brought home to England, and placed in a training school in Wales. Here he worked for three years in apparent health, but at the end of this time the sleeping sickness laid hold of him, and he died. This is a well-authenticated case. The negroes themselves say that a man is never safe from sleeping sickness until seven years have elapsed after a visit to a sleeping sickness district. This prolonged latency is another important fact which I would also ask you to bear in mind as having a bearing on what I shall advance later on about the etiology of this singular disease.

Before proceeding further I will give a summary of what we have been able to learn and observe about our cases. The account is very incomplete, as there are linguistic difficulties which, as you will readily understand, make it difficult to get clear and reliable information about the subjective symptoms as well as about the medical histories of the cases.

Case I.—Eli Mboko, aged about 20, until his present illness began had the reputation of being an exceptionally bright and intelligent lad. He taught himself English, built his own house, and in many other ways displayed an amount of enterprise unusual in a negro. He was regularly employed as a teacher in the Mission School at Mbanza Manteka, a village in the hilly country on the south bank of the Lower Congo, and a notorious haunt of sleeping sickness.

He discharged his duties with ability and energy until about twelve months ago. He then began to be listless and vacant-minded. He would now lie abed in the morning, neglect his work, and cease to take an interest in his former occupations and amusements. Mrs. Richards, who superintended the school, told me that on several occasions she found him standing motionless in the middle of the class-room regardless of what was going on around, and simply gazing into vacancy. When she spoke to him he would rouse himself and resume his work, and presently he would relapse into the same listless, vacant condition. He complained of headache, particularly occipital headache, and at times fever. By May of this year he was quite unfit for work; his gait had become tottery and uncertain, and he drowsed or slept most of the time. He never had any fits or maniacal attacks. He volunteered to come to England, and left the Congo on August 27. He improved somewhat on the voyage, for when I fetched him from Bow on the day of his arrival in London—September 24—though very quiet and reserved, he appeared to be wide awake, taking an interest in the traffic in the streets as we drove along to the

hospital. He was quite able to walk upstairs to Alexandra Ward.

On admission under Dr. Abercrombie he seemed to be in good general health. He was fairly well nourished, and even sleek. Lately, however, he has fallen off somewhat in condition, and his hair and skin have become dry and lustreless. At first his breath was offensive; this has now improved. His appetite and digestion are vigorous. The bowels on admission were constipated — as, indeed, they still are. Microscopic examination showed that the stools contained large numbers of the ova of ascaris lumbricoides, of ankylostoma duodenale, and a few of trichocephalus dispar. The thoracic and abdominal viscera appeared to be healthy. There was no sugar or albumen in the urine. Temperature has ranged from 97° to 99° F., being usually slightly subnormal. Pulse 80 to 90, respirations 20. The blood count gave 5,300,000 per cmm., hæmoglobin 60 per cent. The blood contained no malarial parasites, but filaria perstans was, and is, present in moderate abundance —about 1 filaria in every cmm. The senses were, or appeared to be, normally active. Mr. Treacher Collins, who was good enough to make an ophthalmoscopic examination, found fundus and media perfectly healthy. The pupils were equal and reacted briskly both to light and accommodation. A very few and ill-defined papules could be made out on the skin of the chest and abdomen, but there was no postulation and no marked pruritus. The knee-jerks and other deep and superficial reflexes were active; but his gait was shuffling and feeble, and his hand grasp was markedly impaired. When he walked he progressed slowly, his knees slightly bent. He was easily fatigued, and always seemed glad to sit or lie down. There was no muscular tremor, no local anæsthesia, no paresis. The lymphatic glands, particularly those of the neck, were slightly but distinctly enlarged. In size they varied from an almond to a hazel nut; they were not at all tender.

Since admission his condition has varied very little. For the most part he keeps his bed, lying perfectly still with eyes shut, as if asleep. His face has an expression of deep melancholy, At times he sits up by the fire, but even then he seems to be asleep. The only time he rouses himself thoroughly is when food is brought, or when for a short time he goes on the balcony and watches the traffic in the streets. As a rule he is glad to get back to bed. A touch or a loud sound causes him to open his eyes, so that if he is asleep, the sleep must be a very light one. When spoken to he opens his eyes and answers questions slowly, in few words, and to the point. Even while he is being spoken to, often his eyelids fall as if he were overpowered by an irresistible desire to go to sleep. He never seeks to enter on, or to prolong, a conversation. He rarely smiles; if asked, he says he is very unhappy on account of his drowsiness. Since he entered the hospital he has become distinctly more lethargic, and, I think, has lost flesh and muscular power.

Case II.—Tendo Mkaloo, supposed to be about 11 years of age, comes from the same village, Mbanza Manteka, as Mboko. Very little is known about his antecedents. He is believed to have shown symptoms of sleeping sickness for about two months, that is to say, since May or June, before he left the Congo. During the voyage home he became much worse. When brought to hospital he was in a state of great emaciation and weakness. He could not walk without support, and was barely able to stand alone; he had to be carried upstairs. His cheeks were sunken, his eyes unusually prominent, his lips were swollen and dry, the saliva dribbling constantly from the corner of his mouth; his hair was dry and scurfy, and his skin harsh and lustreless. Arms, abdomen, and chest were streaked with white lines, nail marks from the scratching provoked by an incessant pruritus associated with numerous scaly papules. The superficial lymphatic glands and even trunks were universally enlarged, particularly so those on the back and sides of the neck. Some of the glands appeared to be very tender, for he carried his head stiffly as if movement hurt him, and he shrank and cried when an attempt was made to examine the little swellings distinctly visible at the side of the neck.

His breath was foul, and his abdomen tumid and lax. The spleen was much enlarged, extending as far as the umbilicus; the liver also was enlarged, its lower border being readily felt about a hand's breadth below the costal margin. As in the case of his companion, his fæces contained myriads of ova of ascaris lumbricoides, ankylostoma duodenale, and trichocephalus dispar, and he was markedly constipated.

His temperature was considerably above normal for some days after admission. Eyes, lungs, heart, and kidneys appeared to be healthy.

The superficial and deep reflexes were active. He slept and drowsed almost continuously during the first few days. At first he had to be coaxed to eat, and had often to be fed by the nurse. Sometimes he would fall asleep at his meals. There was some suspicion of muscular tremor.

His blood count gave 4,500,000 per cmm., and a hæmoglobin value of 50 per cent. Filaria perstans was found in considerable abundance—8 per 5 cmm. No malarial parasites were discovered.

After due preparation he had a course of thymol (15 grains for four doses at intervals of an hour and a half); this effectually rid him of his intestinal parasites. Probably partly in consequence of this, partly in consequence of the warmth and good feeding, and partly in consequence of the large doses of arsenic he was put upon, his general health quickly underwent a marked improvement, and his spleen and liver diminished in size. Concurrently with this his drowsiness got less, and he is now much more lively; he even laughs occasionally. He sits up in bed or by the fireside and watches what is going on about him. He is also putting on flesh, and is able to walk about a little, though his gait is slow and shuffling. The pruritus, however, is as bad as, or even worse than, ever. His lymphatics, though diminished in size and no longer painful, are still distinctly enlarged. The prominence of the eyes is less marked; he no longer dribbles from his mouth, and he feeds himself and eats with some appetite. He has had one or two feverish turns, but, as a rule, his temperature is normal or subnormal.

So much has he improved during the few weeks he has been in hospital that we are sometimes tempted to think, were we not assured to the contrary by those familiar with sleeping sickness, that the diagnosis may be wrong. We are told, however, that there can be no doubt the little fellow is the subject of this disease, and that ere long the old symptoms will recur with increased severity, aud that others of graver character will by-and-by be superadded.

From these accounts you will be able to form some idea of the earlier phases of one type at least of sleeping sickness.

Symptoms.

Onset.—A negro, otherwise apparently in good health, is unaccountably smitten with a gradually increasing mental and bodily lethargy which goes on deepening in intensity until he is bedridden. Those who are familiar with the disease, including very often the patient himself, can recognise the earliest threatenings of the impending calamity. There is a characteristic expression of face and body; a significant droop of the upper eyelids; a listless carriage of the body; an indifference to old amusements and occupations; a stolid, rather mournful expression of countenance; perhaps slight puffiness of the features. It is noticed that the patient is easily tired at his work; that he lies long in bed in the morning; that he often falls asleep, even at his work; that he becomes morose and unsociable, and ceases to take share in conversation. Nevertheless he will answer intelligently and to the point when addressed. He may have to be asked once or twice before he replies and the answer when it comes may be a brief one; but, from the appropriate nature of the answers, it is evident that questions are properly, though perhaps slowly, comprehended.

The Sopor.—While you speak to him his eyelids may fall and sleep seemingly overpower him. This is very apparent in the elder of these two boys. If you put the question to this lad he may tell you that he has headache, and he can be got to indicate with his hand the aching part; but he never spontaneously complains of his suffering. People may be talking all around, but apparently he takes no notice of what they are saying, although an unusual noise or a light touch may make him open his eyes for a moment. If he is really asleep at these times the sleep is a light one. The condition seems to be one of mental vacancy rather than one of true sleep.

Muscular Debility.

Equally striking is the muscular debility from which both patients suffer. Their movements are all languid; and they are very easily tired out. Sitting up for an hour or two in a chair in the afternoon thoroughly exhausts them, and they are glad to get back to bed. When they walk they shuffle along, sometimes tottering like one half asleep, or like a drunken man; their knees seem to give way under them.

At first sleeping sickness patients can feed themselves, although they may take a long time over it. The little boy takes an unconscionably long time over dinner. He pauses between each mouthful, gazing into vacancy the while; he has to be reminded now and again that he is dining. Sometimes such patients will fall asleep with the morsel half way to their mouths, or even with the half chewed food between their teeth, and may have to be wakened up to swallow it. At a later stage of sleeping sickness muscular tremor usually sets in; sometimes this is so marked, even at an early stage, that the patient can no longer feed himself.

Early Nervous Symptoms.

The symptoms of the disease, at all events at this stage of its progress, point to a pathological condition of the higher nerve centres only. The knee jerks and other reflexes are intact; there are no bladder nor rectal symptoms; no trophic lesions. The discs and fundi are perfectly normal. Nutrition is not impaired, and digestion and assimilation are satisfactorily performed.

General Symptoms.

From the commencement the patient may be subject to short daily spells of feverishness; or he may have a high temperature for several days on end. Fever, however, is not, as a rule, of an urgent character, unless there is concurrent malaria. Occasionally there may be a little diarrhœa. At other times, and as a rule, the body temperature is subnormal—96° or 97°F. Such patients evidently feel chilly, for they like to coil themselves up in some sheltered spot and bask in the rays of the broiling tropical sun.

Skin Lesions.

A very striking and common symptom in sleeping sickness is the intense pruritis from which many of the patients suffer. It is especially marked on the trunk, but it occurs elsewhere. Little papules can be seen in many places, especially about the chest and abdomen. In healthy young negroes the skin is soft and glossy, like velvet; but in this disease—as is particularly apparent in the younger of these boys—it becomes dry and lustreless, and is generally scored all over with the white streaks produced by the incessant scratching. If you notice the elder of the two boys you will often see him carry his hand to his nose or forehead, and rub the part as if it were irritated.

Enlarged Glands.

Another and interesting feature of sleeping sickness is an enlargement of the lymphatic glands, especially of the posterior cervical. In some instances, as in the smaller boy, less so in the elder boy, most of the superficial glands are affected. The individual gland can readily be felt enlarged to the size of an almond or of a small nut. In the little boy at one time the posterior cervical glands on the right side appeared to be painful, for he would cry when his head was moved; he held his head rather stiffly, apparently in consequence of subacute cervical adenitis.

Progress of the Disease.

For a long time, perhaps for several months, this is about all that can be made out in the type of the sleeping sickness we are considering. Some days the patients seem a little brighter, some days they seem

little duller. Occasionally they become quite active and intelligent; and it may even seem that they have recovered. Such improvement, I am assured, is invariably only temporary; sooner or later the lethargy returns, and the disease once more advances to the inevitable and fatal issue.

Convulsions and Mania.

In certain instances, and by no means rarely—and this is the other type of sleeping sickness I have hinted at—the disease is introduced by, or its progress is interrupted by, maniacal outbursts; not infrequently by epileptiform seizures, very like those of general paralysis of the insane. A whole series of convulsive fits may follow one after the other. The maniacal outbreaks may take very different forms—delusions of all sorts, hallucinations, homicidal or suicidal impulses. These epileptic and maniacal outbursts are supposed to be characteristic of the more acute cases; such cases are believed to advance more rapidly than the purely lethargic ones. I asked Mr. Richards why he did not bring a case of this description home. He told me that it would have been very difficult to have managed such a patient on board ship; that very probably he would have jumped overboard in a maniacal fit, or, at all events, he would have been an intolerable nuisance to his fellow passengers.

Terminal Symptoms.

Whatever may have been the exact characters and progress of the earlier phases of the disease, ultimately the patient becomes completely bedridden. Nutrition now begins to suffer, if it has not done so before. Choreic, convulsive, or tetanic spasms of groups of muscles or, it may be, of a more general character, in addition to the tremor already mentioned, are apt to occur from time to time, indicating grave implication of the motor centres. Muscular prostration is now extreme, torpor more profound and continuous. Bedsores may form, or diarrhœa or other complication set in and carry off the patient, or he may die in one of his convulsive or tetanic seizures. Some years ago there was a case of this disease under Dr. Stephen Mackenzie in the London Hospital. I saw this man when he was dying. For hours his head was violently retracted by tetanic contraction of the extensor muscles of the neck, and every now and again he seemed to be on the point of asphyxia from spasm of the glottis. The disease may run its course in two or three months, or it may last for as many years. Nine months seems to be about an average time.

Pathology.

Although a considerable number of *post-mortem* examinations of cases of sleeping sickness have been recorded, little, if any, light has been thrown by them on the morbid anatomy or pathology of the disease. In some of the records, fulness and even varicosity of the vessels is reported; in other instances the vessels are described as being empty. In some instances the brain substance was said to have been abnormally hard; in other instances abnormally soft. In the earliest recorded *post-mortem* examination the pineal body was found to be enormously enlarged; in subsequent examinations this condition has not been remarked. In Dr. Stephen Mackenzie's case, beyond a cysticercus on one of the anterior lobes of the cerebrum, no morbid lesion of the brain was detected; certainly there was no meningitis, and no gross lesion of the cerebral substance.

Natural sleep, as you are aware, is associated with, and probably depends on, anæmia of the brain. Morbid sopor depends sometimes, apparently, on the direct action of a toxic substance on brain cells; sometimes on a cerebral anæmia produced by the presence of a tumour, or by an action of the toxic substance on the intracranial circulation. In which of these ways the sopor of sleeping sickness is produced it is as yet impossible to say. I have sometimes been tempted to think that perhaps in these cases the pituitary body is the original seat of disease, and that the brain becomes secondarily affected. Such a hypothesis receives some, though I confess very slight, support from experimental physiology as well as from recorded cases of disease of this organ. I can only hope that our cases may yet throw much needed light on the nature of what is at present a pathological puzzle.

[Note.—After the delivery of this lecture I received on October 27 a letter from a friend on the Niger giving some particulars of the *post-mortem* examination of a case of sleeping sickness. The pituitary body was found to be enlarged. There was an old blood clot on or in it, and, as I gather, some cystic formation as well.]

Etiology.

It has often been asked, What is the cause of sleeping sickness? I cannot give any decided answer to that question, but we may very properly seek in the symptoms, distribution, and, so to say, the natural history of the disease for some indication as to this important point.

Sleeping sickness has been attributed to all manner of things, amongst others to sunstroke; but the case I have alluded to as having developed in Wales effectually upsets such an idea; a Welsh sun is not likely to penetrate a negro's cranium. It has also been attributed to the inordinate consumption of palm wine—a common vice in the negro; to excessive venery; to the use of improperly prepared manioc—the staple food of many of the negro tribes, and when improperly prepared apt to be poisonous. Manifestly it can be due to none of these things, for children, who are just as subject to the disease as are adults, do not drink intoxicants, do not indulge in sexual excess; and even negroes, when they visit Wales, do not feed on manioc. In the slave days it was sometimes attributed to nostalgia, to grief at being torn from home and friends; but at the present day, at all events on the Lower Congo, there is nothing of this sort. Like all tropical pathological puzzles, sleeping sickness has been attributed to malaria—that blessed cloak for ignorance; but there are none of the clinical or pathological marks of malaria about the disease. It is true that one of our patients has an enlarged spleen, but the type of the fever he sometimes suffers from is not that of malaria. Moreover, I have examined his blood carefully on several occasions and found no plasmodia, no pigmented leuco-

cytes. The other boy's spleen is not enlarged. In neither is there marked anæmia, such as there is invariably present in pronounced malarial cachexia. Some years ago two Portuguese pathologists declared that they found a specific bacterium in a case of sleeping sickness, and that they communicated the disease to the lower animals by injections of cultures of this bacterium. Dr. Bullock has attempted to grow a bacterium from the blood and lymphatic glands of one of the patients but his flasks have remained sterile. No, sleeping sickness can be attributed to none of these things.

There are some circumstances which, to my way of thinking, seem to suggest a clue that is well worth following up. I have already told you that sleeping sickness is limited to a certain region of Africa. In the endemic districts it attacks old and young, but especially the latter, particularly those between the ages of 10 and 20. It may pick out one or two in a household, or it may attack an entire family. Mr. Richards tells me that he heard on the Congo of an instance in which it was introduced into a hitherto immune village by a case that came from a neighbouring infected village; a circumstance suggesting transmission more or less direct of some form of infection. Indeed, the natives say that it is infectious; they say, doubtless erroneously, that the saliva, which sometimes dribbles from the corner of the mouth, in advanced cases, conveys the disease. All these facts are compatible with and suggest a living contagion.

I have also told you that it may remain latent for many years, and develop ultimately thousands of miles away from the endemic centre—that is, from the spot where its cause was acquired. There are many disease germs which are capable of remaining latent for years, and then of springing into pathological activity—tubercle and leprosy, for example. But, then, these diseases differ from sleeping sickness inasmuch as they are not confined to limited geographical areas; and, moreover, when introduced into virgin populations, being directly communicable like all bacterial diseases, they spread. Sleeping sickness will not spread. Why does it not spread? Manifestly because it depends on certain local conditions, conditions found only in limited districts in West Africa. This implies that these conditions exist only outside the human body; and, moreover, that these conditions cannot be transported.

This further implies that sleeping sickness depends either directly on a food of some sort peculiar to West Africa; or, directly or indirectly, on some plant or animal equally limited in its geographical distribution.

In Nature it is only such things as these that are geographically limited in the way that sleeping sickness is limited. Did it depend on a food—that is to say, on some organic poison in food, it is strange that the manifestations of the poisoning are at times delayed for years. It must therefore depend on some plant or animal. Further, the phenomena of the disease, the prolonged latency especially, demand that the cause must be something which can remain alive, though it may be pathologically inert for a very long time.

Filaria Perstans.

When in difficulties about the explanation of some obscure pathological or other phenomenon, in the absence of a better guide it is perhaps permissible to turn for assistance to analogy. Let us try if analogy will help us in our present dilemma, for there is an *a priori* probability that like diseases are produced by like causes. Let us first formulate precisely what it is we want from analogy. Are there any diseases which, like sleeping sickness, although produced by a living cause, can remain latent for prolonged periods, and which, moreover, can be acquired only in certain limited spots, are not directly infectious, cannot be introduced into virgin districts, and which depend directly or indirectly on the fauna or flora of their endemic areas? Yes; there are malaria, elephantiasis, and many others which I could mention. Why are these diseases so limited? Recent investigations enable us to answer this question. It is because their specific germs—the plasmodium in the one case, and the filaria in the other—before they can enter the body of man have to pass through the bodies of certain of the lower animals, which animals are so constituted that they can live only in certain more or less limited geographical or rather zoological areas.

If this be the case in the diseases mentioned and exhibiting the peculiarities enumerated, the same explanation may apply to other diseases with similar peculiarities. I think, therefore, that the germ of sleeping sickness in this respect resembles that of malaria and that of elephantiasis—that is to say, that at one stage of its existence it must necessarily live in some living host other than man; some animal or plant found only in the equatorial regions of West Africa.

There is one fact about sleeping sickness that greatly encourages this hypothesis, as it fits in exactly with such a view of the etiology of the disease. A peculiar parasite—filaria perstans—has been found in the blood of both the patients which you have seen. Moreover, this same parasite was found in the blood of the other patient whose case was studied in London some time ago—Dr. Stephen Mackenzie's case. The particulars of this case are fully recorded in the Clinical Society's *Transactions*, vol. xliv. In fact, it was in the blood of the latter patient that this parasite was first discovered. Dr. Mackenzie told me that his house-physician (Mr. Fagan) while examining the blood, had found in it what he took to be the ordinary blood worm—filaria nocturna. Dr. Mackenzie remarked, however, that some of the worms appeared to be larger than others, and, knowing that I took an interest in this class of parasite, he asked me to look at them. I procured slides of the patient's blood, and carefully studied the worms. I remarked that the larger worm differed not only in size, but also in shape, in structure, and in habit, from the smaller. You are aware that the ordinary filaria of the blood, filaria nocturna, is an active, wriggling creature, about $\frac{1}{75}$ inch in length by about $\frac{1}{3000}$ inch in breadth; that it has a sharp-pointed tail; that it is enclosed in a loose trailing sheath or sac; that although it wriggles about, it practically remains at one spot on the slide, and does not locomote; and that it comes into the peripheral circulation only during the evening and

night. Now this new worm was only about $\frac{1}{125}$ inch in length by about $\frac{1}{5000}$ inch in breadth; it had a blunt tail; it had no sheath; besides wriggling about, it travelled through the blood on the slide, often at a great rate; further, it was present in the peripheral circulation at all hours of the day, as well as of the night. Manifestly it was a new species.

Naturally enough the concurrence of a strange parasite in a strange disease suggested, though it by no means proved, a cause-and-effect relationship between the two. Accordingly I set to work to find out something more about this new worm, among other things its geographical range, its degree of prevalence, and if it were invariably, or often, present in sleeping sickness. I procured slides of blood from hundreds of natives from different parts of Africa and of the tropical world. I found that it was only in slides procured from Congoland and from one or two other parts of West Africa that filaria perstans occurred. It does not occur, as far as I have been able to ascertain, in Egypt, in East Africa, or in South Africa. I also obtained strong evidence that it does not occur in Dahomey, nor in the Illorin district in the Niger bend, districts where, although well within the geographical limits of sleeping sickness, that disease does not originate. I also found this filaria in blood sent me from cases of sleeping sickness on the Lower Congo. But when I came to investigate the degrees of prevalence of filaria perstans in its geographical area, I seemed to find too much. I found that quite 50 per cent. of the healthy inhabitants of Congoland and of some other West African places harboured this parasite. This fact of course told against the theory that the new filaria stood in causal relationship to sleeping sickness. After all, their relationship might only be one of concurrence—a very different thing from cause and effect. In other respects, however, the new filaria seemed to fulfil all the requirements. It could be acquired only in a very limited area; it could be carried in a patient's body and live in a foreign country for years. I found it in the blood of a negro who had not been near Africa for over six years. Like other parasites of its class it could very well exist without causing disease. From its nature we know that it cannot spread by direct infection, but that it must first pass through the body of another animal; and, for the same reason, that it cannot be introduced and become domiciled in a virgin country where this other intermediate animal does not occur. We come to this then, that though there are some facts pointing to an intimate relationship between the parasite and the disease, yet the extreme frequency of filaria perstans, and the relative rarity of sleeping sickness in the endemic area seem to be strong arguments against this parasite being the cause of the disease.

At the same time we must bear in mind that there are many parasites which, though sometimes pathogenic, are nevertheless generally innocuous. Filaria nocturna, for example, does not by any means always give rise to elephantiasis; the cysticercus does not always become lodged in the vitreous humour and destroy the eye; distoma Ringeri does not always stray to the brain and cause Jacksonian epilepsy; hydatids do not always produce disease of the lungs or liver; so it may be with filaria perstans. It might very well be that it is only in a certain possibly small proportion of instances that it gets into a position to damage the encephalon. Similar parasites are known to be great travellers and to hunt each other, as it were, through the tissues of the body. Filaria loa, for example, may be felt one day in the connective tissue of a finger, and a few days later may be crossing the eye under the conjunctiva; in fact, it can be seen thus travelling about. The guinea-worm is also a notorious traveller; so are the young trichina and hundreds of other parasites. It is therefore quite in conformity wtth the teachings of analogy that filaria perstans may occasionally wander into some tissue, either in the brain or connected with the brain, and so in certain individuals set up serious cerebral disease, whilst in other and in the majority of cases it does not do so. This is quite conceivable. The fact of the presence of filaria perstans in a large proportion of people who may never suffer from sleeping sickness is therefore not an insuperable obstacle to accepting it as a cause of this disease.

There are several other facts, however, which seem to militate against this hypothesis. There may be an explanation for them, and the hypothesis suggested by geographical distribution and the presence of filaria perstans in so many instances of sleeping sickness may be perfectly correct; nevertheless, I think it right to mention that filaria perstans occurs, apparently, all over the Congo valley, while sleeping sickness is confined to certain villages and districts; moreover, it tends to occur in outbreaks which from time to time assume epidemic characters. If filaria perstans be the cause of sleeping sickness, we should expect the distribution of the disease to be in closer conformity than it seems to be with the prevalence of the parasite.

Then in sleeping sickness the lymphatic glands, as I have mentioned, are frequently enlarged. It is difficult to see how this clinical fact is to be explained on the supposition that the parasite acts pathologically primarily on the encephalon.

The pruritus, which is so marked a symptom in the disease, may be the expression of a neurosis; still, for this clinical phenomenon also, such an explanation is not entirely satisfactory.

If filaria perstans be not the cause of sleeping sickness I cannot suggest any other cause. There are sufficient grounds, at any rate, for regarding it as a possible cause, and for following up the clue which its occurrence in this disease clearly affords.

Conclusion.

The working hypothesis suggested by the facts—analogical, clinical, and experimental—is to this effect: That the germ of sleeping sickness operates primarily on the encephalon; that this germ is possibly filaria perstans; that the parasite in its wanderings, either by entering the brain, or by interfering more or less directly with its nutrition, may gradually bring about a cessation of its function, ultimately leading to secondary neuro-muscular malnutrition and symptoms of sleeping sickness. If it can be shown that filaria perstans is the cause of sleeping sickness, the next

step will be to ascertain the life-history of this parasite outside the human body; this once known, it will become easy to indicate an efficient prophylaxis.

Treatment.

Sleeping sickness, so far, has proved incurable. The natives in some places excise the enlarged cervical glands. When such an operation has been followed by apparent recovery, doubtless there has been a mistake in diagnosis. I heard of what appeared to be a case of incipient sleeping sickness which was cured by large doses of arsenic; in this case, also, diagnosis may have been at fault. In the early stages of the disease purgation and tonics, the clearing out of intestinal parasites, and similar subsidiary measures, do good temporarily. The younger of our patients certainly derived benefit from a liberal dosing with thymol; it rid him of a large number of round worms and ankylostomata. At present he is rather better than when he entered the hospital, but we may not expect ultimate recovery. Some time ago hypodermic injections of testicular fluid seemed to give encouraging results in certain cases on the Congo; later experience, however, has not been favourable to this remedy. At present our elder patient is taking a preparation of pituitary gland. The younger is on arsenic, which we propose to push. I am bound to say that though I hope for permanent benefit from these measures, I am very far from expecting it.

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THE UNCLASSIFIED FEVERS OF HOT CLIMATES.

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In order that a discussion such as I have now the honour to introduce may be pursued with profit, it is necessary, I think, to define its object and limit its scope; and this seems to be the chief purpose which I ought to hold in view in this paper. It may at first sight seem a somewhat elusive one because of the fluid character of the phenomena which we are met to consider, namely, the unclassified fevers of India—a title which implies that they are undefined, if not undefinable—and it may seem paradoxical to attempt to classify fevers which are grouped under such a heading. But it appears to me to be impossible to move a step in this discussion without making at least a provisional classification of these fevers, and placing them with reference to other fevers of a more definite and settled character. Such an attempt is absolutely necessary in order that those who take part in the discussion may have a clear conception of what fevers are included among the unclassed groups, and may make use of the same terms with regard to the same phenomena. When this is done it will probably be seen that there is really no great fluidity, and that certain fairly well-defined febrile phenomena crystallise out, which it will be possible to weigh and discuss.

A study of what has been written by the older authorities shows that they also grappled with the fevers of warm climates, and were able to divide them into clinical groups, though it is not always easy to follow the language in which they express themselves. But since their time certain fevers have been completely separated from the rest, and our task, that of analysing the residue, has by so much become comparatively easy.

In the time of Annesley and Twining the great division between enteric fever and typhus had not yet been clearly distinguished, and they and their contemporaries were not able to separate with precision typhoid, which existed in their day much as it does now, from the continued and remittent forms of malarial fever; though it is evident that both of these writers, and especially Twining, saw that certain cases of fever occurring in the cold season differed from other continued or remittent fevers by their insidious course, and by the presence of what we now know were the characteristic lesions of typhoid. There is now comparatively little difficulty in distinguishing typical typhoid from the other fevers with which it was formerly confounded in Europe as well as in India.

The older writers, again, did not have at their disposal the diagnostic and curative effects of quinine to help them; and these, together with the recent discovery of the malarial parasite, place us in a position of the greatest advantage in the task of sorting out malarial from other fevers; and, thirdly, we have the further advantage of the work of Bruce, Gipps, and Hughes, who have opened our eyes to the existence of Malta fever as a distinct clinical entity, possibly of wide distribution.

It is with the residue left by these workers that I propose to deal to-day, and the object to be gained, at least to be aimed at—and, no doubt, ultimately gained—is to focus the attention of pathologists on these other groups of fever which seem to some of us to be equally well defined clinically, and to be calling for investigation.

In order to show the place in nature which these unclassified fevers seem to occupy, I have drawn up a provisional classification of the fevers met with in the tropics and placed them in it in the position into which they seem to fall most naturally—though, of course, further study will no doubt modify our conceptions with regard to them very considerably.

A Provisional Scheme Showing the Probable Position of the Classified Fevers of India:

I. Non-specific fevers of doubtful causation, probably climatic:—
- (*a*) Ephemeral fever.
- *(*b*) Common continued fever.
  - (1) Febricula,
    - var. Nakra, or nasha fever.
  - (2) Simple continued fever.
  - *(3) Ardent fever.
- *(*c*) Thermic fever, siriasis, heat apoplexy.
- *(*d*) "Low fever."

II. Specified fevers, of known or unknown origin:—
- (1) Aphthous fever.
- (2) "Milk sickness."